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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,080	01/03/2002	Peter C. Isakson	2891/3 (PHA 4142.2)	7358

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EXAMINER	
EPPERSON, JON D	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/17/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
File Copy	10/038,080	ISAKSON ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Please note: The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1639.

Status of the Application

1. The Response filed March 19, 2003 (Paper No. 12) is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-4 and 6-9 were pending in the application (claim 5 was withdrawn from consideration by the examiner as being drawn to a non-elected species pursuant to 37 CFR 1.142(b), see Paper No. 9, paragraph 5). Applicants amended claims 1-9 (see Paper No. 12). Therefore, claims 1-4 and 6-9 are pending and examined on the merits in the present case.

Withdrawn Objections/Rejections

4. With respect to the rejections under the second paragraph of 35 U.S.C. 112, the rejections denoted A-D are withdrawn in view of applicant's amendments to the claims and/or arguments. The "Enablement Rejection" under 35 USC 112, first paragraph, is withdrawn in view of

Applicants' amendments and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

5. Claims 1-2, 6-9 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These are genus claims. For example, claim 1 discloses a "therapeutically-effective" combination of a "cyclooxygenase-2 selective inhibitor" and a "selective leukotriene B_4 receptor antagonist." The scope of this claim includes an infinite number of "combinations" of an infinite number of "cyclooxygenase-2-inhibitors" and an infinite number of "leukotriene B_4 receptor antagonists" wherein no distinguishing structural attributes are provided for either the "cyclooxygenase-2-inhibitor" or the "leukotriene B_4 receptor antagonist." The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form either the "selective cyclooxygenase-2-inhibitor" or the "selective leukotriene B_4 receptor antagonist." Although the specification discloses many possible examples for both the "cyclooxygenase-2 selective inhibitors" and the "selective

leukotriene B_4 receptor antagonist" and there are many examples known in the literature (see Claims 2-9, pages 5-12; see also 35 USC 102/103 rejections below), the specification and claims do not provide ***any*** guidance as to what structural features ***all*** of these compounds share. Consequently, it is not possible to determine *a priori* which compounds would be "selective leukotriene B_4 receptor antagonist" or "cyclooxygenase-2 selective inhibitors" because there is no common structural attributes that can link together ***all*** of the compounds i.e., the "selective leukotriene B_4 receptor antagonists" or the "cyclooxygenase-2 selective inhibitors." There is no teaching that would allow a person of ordinary skill in the art to determine *a priori* ***all*** the different types of compounds that should be included in this genus from the examples provided by applicants.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing examples Taisho NS-398, Merck MK-966, etc. that are known in the literature (see specification, claim 2) is insufficient to teach the entire genus. In other word, Applicants must provide some correlation between the structure and function of the claimed compounds (See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 1013 (Fed. Cir. 2002) wherein the court adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently

detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics ***when coupled with a known or disclosed correlation between function and structure*** ... ." *Enzo*, 296 F.3d at 1324-25 (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). Thus applicants' claimed scope represents only an invitation to experiment regarding other possible "leukotriene B4 receptor antagonists" and "cyclooxygenase-2-inhibitors." Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

Response

6. Applicant's arguments directed to the above written description rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues that [1] the specification provides over 100 examples of compounds that selectively inhibit cyclooxygenase-2 and over 40 examples of compounds that are selective leukotriene B_4 receptor antagonists and, as a result, Applicants' disclosure "cannot fairly be deemed to fall short of the 'representative' number [of examples] required by the MPEP" (see Paper No. 12, page 17, second to last paragraph), [2] "it is not required that an applicant disclose 'all' features possessed by each possible member of a genus for purposes of satisfying the written description requirement" (see Paper No. 12, page 18, paragraph 1), [3] there are

examples in the case law where functional language has been used including *In re Fuetterer* and *In re Herschler*. For example, Applicants put forth that in *In re Herschler* written description of chemical compounds need to be "only so specific as to lead on having ordinary skill in the art to the class of compounds" (see Paper No. 12, page 19, paragraph 1), [4] "Moreover, in *In re Herschler*, claims were directed to "a physiologically active steroidal agent" as a class of chemical compounds where the specification detailed only 1 example. In the instant case, the specification provides over 100 examples of compounds that selectively inhibit cyclooxygenase-2 and over 40 examples of compounds that are selective leukotriene B_4 receptor antagonists. If the CCPA determined that a functional description and one example satisfied the written description requirement, applicants' functional description plus 100 and 40 examples ... cannot fairly be deemed to be an insufficient description" (see Paper No. 12, page 20, paragraph 1).

This is not found persuasive for the following reasons:

The Examiner contends that [1] Applicants' ~100 Cox-2 inhibitors and ~40 leuoktriene B_4 receptor antagonist would not be enough examples to show that Applicants were in possession of a genus that would include an infinite number of compounds with no shared core structure (i.e., no correlation between the structure and the function), [2] The Examiner has never stated that "all" features of every possible member need to be disclosed. The Examiner only contends that when Applicants use "functional language" to describe their claimed invention that Applicants must also provide a "correlation between the function and structure" as set forth in MPEP § 2163(II)(3)(a)(ii) because without such a correlation a person of skill in the art would not know what compounds to test. See also *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 1013 (Fed. Cir. 2002) wherein the court adopted the standard set forth in the Patent and

Trademark Office ("PTO") Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics ***when coupled with a known or disclosed correlation between function and structure*** ... ." *Enzo*, 296 F.3d at 1324-25 (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). No such "coupling" of structure and function has occurred here.

Furthermore, [3] these cases are not on point because they do not encompass Cox-2 inhibitors or Leukotriene B_4 antagonists, which are the subject matter of the present case. A case that is more on point is *University of Rochester vs. G.D. Searle & Co., Inc.*, 249 F.Supp.2d 216, 175 Ed. Law Rep. 539 W.D.N.Y., 2003 wherein the Court held that "selective Cox-2 inhibitors" lack written description when described only in functional terms without a correlation between structure and function.

In addition, even assuming *arguendo* that the standards set forth in *In re Fuetterer* and *In re Herschler* apply to the present case, a person of skill in the art would still not reasonably conclude that Applicants were in possession of the full scope of the claimed invention because Applicants have not provided any guidance as required by *In re Herschler* that would "lead one having ordinary skill in the art to ... [a] class of compound" i.e., there is no teaching or correlation that would allow a person of skill in the art to determine *a priori* ***all*** the different "classes of compounds" that should be included in this enormous genus. See also *University of Rochester vs. G.D. Searle & Co., Inc.*, 249 F.Supp.2d 216, 175 Ed. Law Rep. 539 W.D.N.Y.,

2003 wherein the court sets forth at length why case law like *In re Herschler* is not contrary to the standards set forth above. See also *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Here, the court stated that "[a]n adequate written description of a DNA ... 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566 (quoting *Fiers*, 984 F.2d at 1171). Although directed to DNA compounds this holding would be deemed to be applicable to any compound or a generic of compounds; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the compound or generic(s).

Finally, [4] the Examiner contends that *In re Herschler* is distinguishable from the present case because the "structure" of a steroidal agent can be immediately envisioned and/or ultimately obtained whereas the structure of a Cox-2 inhibitor or a leukotriene inhibitor cannot.

Accordingly, the written description rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 102

7. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Buchmann et al (US Pat. No. 5,559,134) (Filing Date is **March 23, 1995**; Date of Patent is **September 24,1996**).

For ***claim 1***, Buchmann et al discloses a discloses "new leukotriene-B_4 derivatives [antagonists] ... used in combination ... with cyclooxygenase inhibitors (see Buchmann et al, page column 7, lines 58-65; see also title), which anticipates claim 1. Although the compounds in the Buchmann et al reference do not explicitly state that they are

"selective" inhibitors and/or antagonists they share a reasonably close correlation to the structures that are taught in Applicants' disclosure. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Buchmann et al (WO94/04522) (Publication Date is **March 3,1994**) (Please note: this reference has the same translation as that of U.S. Patent No. 5,559,134 cited above).

For ***claim 1***, Buchmann et al discloses a discloses "new leukotriene-B4 derivatives ... used in combination ... with cyclooxygenase inhibitors (see Buchmann et al, page column 11, lines 58-65), which anticipates claim 1. Although the compounds in the Buchmann et al reference do not explicitly state that they are "selective" inhibitors and/or antagonists they share a reasonably close correlation to the structures that are taught in Applicants' disclosure. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and

the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Response

9. Applicant's arguments directed to the above 35 U.S.C. § 102 (b) and (e) rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues that the newly amended claims are now directed toward "selective" cyclooxygenase-2 inhibitors and leukotriene B_4 receptor antagonists and that the Buchmann et al.'s do not disclose cyclooxygenase-2 "selective" inhibitors and, as a result, the Buchmann et al.'s do not anticipate the claimed invention (see Paper No. 12, pages 23-24).

This is not found persuasive for the following reasons:

The Examiner contends that [1] it is not clear what is and what is not a "selective" inhibitor and, as a result, the Examiner contends that the compounds disclosed by the Buchmann et al.'s would fall within the scope of Applicants' claims (see 35 U.S.C. 112, second paragraph rejection below), [2] even if assuming *arguendo* that Applicants functional definition is clear, Applicants have not set forth any evidence that would indicate that compounds in the Buchmann et al.'s would not be "selective" inhibitors and the Patent Office does not have the facilities to test these compounds (see newly amended rejections above).

Accordingly, the 35 U.S.C. 102 (b) and (e) rejections cited above are hereby maintained.

Claim Rejections - 35 USC § 103

10. Claims 1-4 and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ducharme et al (US Pat. No. 5,474,995) (Filing Date is **January 10, 1994**; Date of Patent is **December 12, 1995**) (IDS Reference Number 60) and Rainsford, K. D. (Rainsford, K. D. "Leukotrienes in the pathogenesis of NSAID-induced gastric and intestinal mucosal damage" *Agents and Actions* **1993**, 39(Spec. Conf. Issue), C24-C26).

For ***claims 1-4 and 6-9***, Ducharme et al teaches cycloxgenase-2 inhibitors and pharmaceutical compositions thereof with compounds of Formula I (see Ducharme et al i.e., "1 of 2", Summary of Invention; see also Ducharme et al "2 of 2", showing various compounds that fall within the scope of Formula I). For example, Ducharme et al teaches a Cox-2 inhibitory (see Ducharme et al, "2 of 2", page 3, RN 157671-80-2) with the same formula as that claimed by applicants in Formula I of claim 2 wherein R^2 is an methyl, A is a furan ring (i.e., furyl), R^1 is a phenyl substituted with a fluoro, and R^3 is a hydrido (Please note that other examples also exist as shown throughout Ducharme et al, "2 of 2"). Ducharme et al also teaches that the above compounds of formula I "will be useful as a partial or complete substitute for conventional NSAID's in preparations wherein they are presently co-administered with other agents or ingredients" (see Ducharme et al, "1 of 2", column 7, lines 65-67).

The prior art teachings of Ducharme et al differ from the claimed invention as follows:

For **claim 1-4 and 6-9**, Ducharme et al is deficient in that although it states that the Cox-2 inhibitors of formula I "will be useful as a partial or complete substitute for conventional NSAID's in preparations wherein they are presently co-administered with other agents or ingredients" (see Ducharme et al, "1 of 2", column 7, lines 65-67), Ducharme et al does not explicitly state that NSAID's are presently co-administered with the leukotriene B_4 antagonists disclosed by applicants. Hence, Ducharme et al is deficient in that it does not teach that the Cox-2 inhibitors of formula I "will be useful" as "substitutes" for NSAID's in preparations where NSAID's and leukotriene B_4 antagonists are co-administered, which would make the required "combination" of Cox-2 inhibitors and leukotriene B_4 antagonists.

However, Rainsford teaches that the leukotriene B_4 receptor antagonist, MK-886, can be beneficially co-administered with NSAIDs (see Rainsford, abstract) ("Gastric and intestinal mucosal lesions by NSAIDs were prevented by both prior (2-5 h) + 0.25 or 0 h oral dosing of the 5-lipoxygenase inhibitor, MK-886", which are identical to figure 2 and similar to figure 10 of the specification). Hence, the combined teachings of Ducharme et al and Rainsford would teach a "combination" of Cox-2 inhibitors of formula I (i.e., Cox-2 inhibitors are "substituted" for the NSAIDs) with leukotriene B_4 receptor antagonists like MK-886. Furthermore, it would have been obvious to use other "known" Cox-2 and Leukotriene B_4 antagonists as outlined in claims 4, 8 and 9 because they would have the

same effect i.e., they would also be Leukotriene B_4 antagonists or Cox-2 inhibitors and thus would have the same therapeutic value when used in combination.

It would have been obvious to one skilled in the art at the time the invention was made to "substitute" the compounds of formula I as taught by Ducharme et al for the NSAIDs in the preparations containing both NSAIDs and leukotriene B_4 antagonists (i.e., MK-886) as taught by Rainsford because Ducharme explicitly states that "compounds of formula I, will be useful as a partial or complete substitute for conventional NSAID's in preparations wherein the are presently co-administered with other agents or ingredients" (see Ducharme et al, column 7, lines 65-67). Furthermore, one of ordinary skill in the art would have been motivated to use the Cox-2 inhibitors and Leukotriene B_4 inhibitors to further lower the gastric mucosal lesions that occur with NSAIDs, while still maintaining the therapeutic effects (see Ducharme et al, column 7, lines 50-65) ("By virtue of its high cycloxygenase-2 (COX-2) activity and/or its selectivity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1) as defined above, compounds of formula I will prove useful as an alternative to conventional non-steroidal anti-inflammatory drugs (NSAID'S) particularly where such non-steroidal anti-inflammatory drugs may be contra-indicated such as in patients with peptic ulcers").

Response

11. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified

from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues that [1] the Ducharme et al does not disclose combining a cyclooxygenase-2 selective inhibitor and a selective leukotriene B_4 receptor antagonist as required by claim 1 (see Paper No. 12, page 25, paragraph 1), [2] Rainsford does not disclose combining a cyclooxygenase-2 selective inhibitor and a selective leukotriene B_4 receptor antagonist as required by claim 1 (see Paper No. 12, page 25, paragraph 2), [3] the combined references teach away from the claimed invention because "Rainsford discloses that the purpose of administering the leukotriene B_4 receptor antagonist with the NSAID is **to reduce gastrointestinal damage** ... Ducharme et al. disclose that a benefit of cycloxygenase-2 selective inhibitors ... is that [they] have 'diminished ability to induce' ... gastrointestinal side effects [i.e., they also **reduce gastrointestinal damage**]. As such, one following Ducharme's instruction to use cycloxygenase-2 selective inhibitors would have no need to follow Rainsford's suggestion to add a leukotriene B_4 receptor antagonist to prevent gastrointestinal damage" and, as a result, there is no motivation to combine the references (see Paper No. 12, page 26, paragraph 1), [4] Ducharme et al "conspicuously fail" to suggest administering cyclooxygenase-2 selective inhibitors with leukotriene B_4 receptor antagonists. The examples and preferences disclosed in a prior art reference must be considered, and can provide sufficient teaching away to defeat an inference of obviousness" (see Paper No. 12, pages 26-27), [5] "In view of the lack of motivation to make the stated combination, it is respectfully submitted that the proposed combination amounts to an impermissible hindsight reconstruction of the elements of applicants' claims using applicants' claims as a guide." (see Paper no. 12, page 27, paragraph 2).

This is not found persuasive for the following reasons:

The Examiner contends that [1-2] one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986), [3] the combined references do NOT teach away from the claimed invention nor do they defeat the inference of obviousness. The fact that both compounds reduce side effects such as gastrointestinal damage would not preclude their use together as purported by Applicants. To the contrary, a person of skill in the art would look to use BOTH compounds together to "further" reduce said side effects than could be reduced by either compound when administered alone (e.g., the fact that one compound reduces a side-effect by 50% would not preclude a person of skill in the art from using another compound simultaneously to try to reduce the side effect even further to say 0 % because if a person of skill in the art would want to reduce a side effect it stands to reasons that they would want to continue to reduce said side effect until it is gone), [4] if Ducharme et al taught administering cyclooxygenase-2 selective inhibitors with leukotriene B_4 receptor antagonists it would be a solid 35 USC § 102(b) reference, not a 35 USC § 103(a) reference. The fact that an element of a claim is not disclosed a "preferred embodiment" does not make it any less obvious.

Finally, [5] in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071,

5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, as stated in the rejection above there is explicit motivation to combine because it would have been obvious to "substitute" the compounds of formula I as taught by Ducharme et al for the NSAIDs in the preparations containing both NSAIDs and leukotriene B_4 antagonists (i.e., MK-886) as taught by Rainsford because Ducharme explicitly states that "compounds of formula I, will be useful as a partial or complete substitute for conventional NSAID's in preparations wherein the are presently co-administered with other agents or ingredients" (see Ducharme et al, column 7, lines 65-67). Furthermore, one of ordinary skill in the art would have been motivated to use the Cox-2 inhibitors and Leukotriene B_4 inhibitors to further lower the gastric mucosal lesions that occur with NSAIDs, while still maintaining the therapeutic effects (see Ducharme et al, column 7, lines 50-65) ("By virtue of its high cycloxygenase-2 (COX-2) activity and/or its selectivity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1) as defined above, compounds of formula I will prove useful as an alternative to conventional non-steroidal anti-inflammatory drugs (NSAID'S) particularly where such non-steroidal anti-inflammatory drugs may be contra-indicated such as in patients with peptic ulcers").

Furthermore, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge

gleaned only from the applicant's disclosure (as noted above wherein the "motivation" to combine the references was outlined using only prior art references), such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Double Patenting

12. Claims 1-4 and 6-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,136,830. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the referenced patent are essentially drawn to same type of "combinations" of therapeutic compounds as the present application. For example, U.S. Patent No. 6,136,830 claims "combinations of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor" (see U.S. Patent No. 6,136,830, claim 1) whereas the present application claims "combination[s] ... of a cycloxgenase-2 inhibitor and a leukotriene B_4 receptor antagonist" (see present application, claim 1). However, applicants claim in many cases the same compounds for both "combinations" (see claim 2 of the U.S. Patent No. 6,136,830 wherein "Bayer Bay-x-1005" is claimed as a 5-lipoxygenase inhibitor; see also claim 3 of the present application wherein the same "Bayer Bay-x-1005" compound is claimed as a leukotriene B_4 receptor antagonist; furthermore, both applications claim compounds with general formula I wherein A is a pyrazolyl as the Cox-2 inhibitor i.e., see claim 2 of U.S. Patent No. 6,136,830 and claim 7 of the present application. Accordingly it is deemed that the inventions claimed herein and that of the patent are obvious variants of each other.

Response

13. Applicant's arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons.

Applicant argues that they have filed a terminal disclaimer disclaiming the amount of any patent term on a patent issuing from this application which extends beyond the patent term of U.S. Patent No. 6,136,839 in order to obviate the rejection.

This is not found persuasive for the following reasons:

The Examiner contends the application/patent which forms the basis for the double patenting rejection is not identified in the terminal disclaimer.

Accordingly, the double patenting rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

Claim 8 was amended in Paper No. 12. However, applicant did not show where support for the newly added compounds (e.g., see Paper No. 12, underlined compounds on pages 35-42). If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02. Therefore, claim 8 and all claims from which 8 depends represent new matter.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1-4 and 6-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-4 and 6-9 are rejected because the compounds in these claims are not defined with any chemical or physical characteristic, but only by functional properties i.e., that they are either a "cyclooxgenase-2 selective inhibitor" or a "selective leukotriene B_4 receptor antagonist." A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention. A person of skill in the art cannot immediately envision all the possible chemical structures for a compound with this function. See *ex parte Pulvari* (POBA 1966) 157 USPQ 169. Here,

the Examiner contends that no correlation between structure and function has been presented for either the Cox-2 inhibitor or the leukotriene B_4 receptor antagonist and, as a result, a person of skill in the art would not be able to "immediately envision all the possible chemical structures" for either the Cox-2 inhibitor or the leukotriene B4 receptor, which is further supported by the widely varying structures claimed by Applicants. Furthermore, Applicants have not set forth the conditions under which the "selective activity" is to be measured further compounding the problem. Thus, the metes and bounds of the claimed invention cannot be determined.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D. Epperson, Ph.D. whose telephone number is (703) 308-2423. The examiner can normally be reached on Monday-Thursday from 9:30 to 7:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon D. Epperson, Ph.D.
June 14, 2003

BENNETT CELSA
PRIMARY EXAMINER